

Original Articles

The prevalence and clinical significance of pulmonary infection due to non-tuberculous mycobacteria in Hong Kong

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An unexpected increase in positive sputum cultures of non-tuberculous mycobacteria (NTM) was noted in Hong Kong in 1990 compared to previous years, in contrast to a steady decline in the number of positive cultures of *Mycobacterium tuberculosis*. A retrospective case note study was therefore undertaken to ascertain the clinical importance of the rise in NTM isolates. A representative sample of 183 of the 675 patients with NTM isolates from sputum during 1990 was identified. Cases were assigned to groups according to whether there was evidence of progressive pulmonary disease due to NTM (group 1), persisting colonization without evidence of progressive disease (group 2) or transient isolation of NTM without evidence of progressive disease (group 3).

Of 168 cases with adequate clinical and radiological records, 28 (16.7%) represented progressive disease due to NTM and 6 (3.6%) represented persisting colonization. The remainder were both transient and clinically insignificant.

Most patients (71%) with progressive pulmonary disease due to NTM had pre-existing lung damage, and 50% had received anti-tuberculous therapy for documented *M. tuberculosis* previously. The commonest organism involved was the *M. avium* complex.

Eighty-six percent of patients with progressive disease and 83% of those with persisting colonization had at least one smear positive sputum specimen, whereas only 2% of patients with sputum contamination had a smear positive sputum sample ($P<0.0001$).

M. malmoense, *M. xenopi* and *M. fortuitum* all appear to be rare causes of significant NTM disease in Hong Kong. However, *M. chelonae* caused four cases of progressive disease within the study population, two of which were fatal.

Although positive sputum cultures of NTM are relatively common in Hong Kong, the majority do not appear to represent clinically significant infection. The spectrum of organisms identified differs from that reported in other regions of the world.

Introduction

Despite advances in treatment and improvements in living conditions, infection with *Mycobacterium tuberculosis* remains a significant problem in Hong Kong with annual notifications of 6500–7000 in the last 5 years (1). Laboratory culture of a large number

of sputum specimens for *M. tuberculosis* results in the isolation of several types of atypical, or non-tuberculous, mycobacteria (NTM). The prevalence of clinical infection due to these organisms throughout the world is uncertain (2); the published figures of NTM prevalence are often incomplete, and do not distinguish between laboratory isolation and true disease due to NTM (3).

The care of patients with tuberculosis in Hong Kong is largely outpatient based, and carried out by Government-run chest clinics and specialist hospitals. A central laboratory processes all specimens from the

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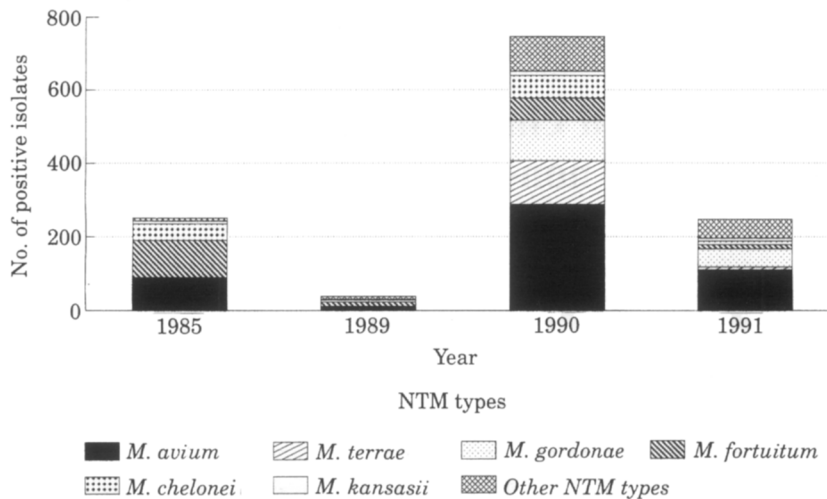


Fig. 1 Numbers of NTM isolates per year in Hong Kong 1985–1991. Six commonest isolates shown.

Chest Clinics, and provides a reference service for NTM isolates from other hospitals. In this way, one laboratory deals with all samples of NTM from the whole of Hong Kong.

A marked increase in numbers of isolates of NTM was noted in 1990 compared to 1985 and 1989 (Fig. 1), the two most recent years for which accurate figures were available. Over the same period (1985–1990) there was in comparison a steady decline in the numbers of positive cultures for *M. tuberculosis* (1). The unexplained rise in NTM isolates in 1990 prompted a retrospective case-note study to determine the importance of these isolates in causing disease, and to investigate the outcome of patients with pulmonary disease.

Patients and Methods

All laboratory cultures of non-tuberculous mycobacteria (NTM) from the central TB laboratory at Yung Fung Shee Memorial Centre during 1990 were identified. Case notes and radiographs were obtained of patients with positive sputum cultures for NTM who were attending three of the largest chest clinics, each representing a different region of the territory (Wanchai Chest Clinic for Hong Kong Island, Kowloon Chest Clinic for the Kowloon Peninsula, Kwai Chung Chest Clinic for the New Territories). Notes from inpatients attending one of the specialist TB hospitals (Ruttonjee Hospital) were also obtained.

Following a review of the case notes and radiographs, patients were assigned to one of four

groups according to whether the NTM isolates were considered clinically significant, and on whether there was evidence of clinical and radiological disease progression. The latest guidelines from the American Thoracic Society on diagnostic criteria (4) for lung disease caused by NTM were used to confirm infection. Briefly, two or more separate sputum samples showing moderate or heavy growth of NTM on culture were required in patients with a progressive cavitary infiltrate on chest X-ray in the absence of other reasonable cause for the disease. Patients with non-cavitary disease did not receive 2 weeks anti-tuberculous therapy prior to repeat culture (4), therefore evidence of persistently positive cultures over a period of at least 3 months in association with progressive disease was required.

Patients in group 1 fulfilled the criteria for progressive pulmonary disease due to NTM (progressive disease). Group 2 consisted of patients where isolation of NTM was persistent but not considered clinically significant because of absence of disease progression without anti-tuberculous therapy (colonization). Patients in group 3 had only transient isolation of the organism with subsequent negative sputum cultures and no evidence of disease progression (contaminant). Group 4 consisted of patients with insufficient evidence to determine whether significant infection was present, either due to inadequate numbers of positive cultures or insufficient follow-up data. A minimum follow-up period of 9 months was considered necessary to determine whether infection was progressive or not. However, in most cases, follow-up was considerably longer

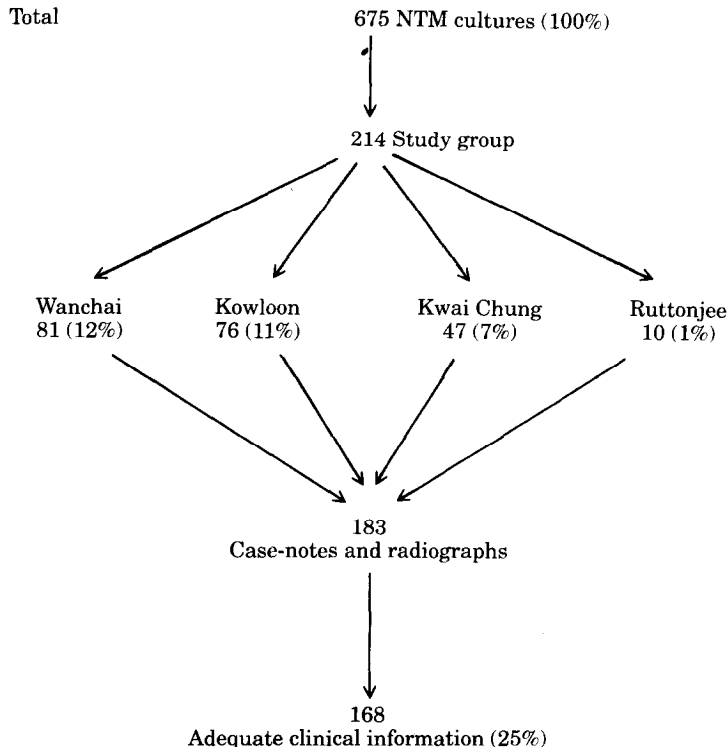


Fig. 2 Numbers of patients with positive cultures for NTM in Hong Kong during 1990 — source of patients. The 675 NTM isolates represent 18% of all *Mycobacterial* isolates during 1990.

than this especially in groups 1 and 2, because many patients had repeated positive sputum cultures over several years.

All sputum samples were cultured on Lowenstein-Jensen culture medium. For identification of *M. tuberculosis*, methods included growth at 25°C, pigment production, niacin test, nitrate reduction test and sensitivity testing to Paranitrobenzoic acid (5,6). This protocol is similar to the British MRC method. For identification of NTM the conventional chemical method and protocol used by the Mycobacteriology Branch of the Centre for Disease Control (CDC) was adopted (5).

Results

Positive sputum cultures of NTM were identified from 246 patients in 1985, 38 patients in 1989, and 675 patients during 1990 (Fig. 1). There were a further 62 isolates from extra-pulmonary sites in 1990. In comparison, there were positive cultures of *M. tuberculosis* from 3001 patients during 1990 (53.4/100 000 population).

Of the 675 NTM isolates in 1990, 214 (32%) came from the Wanchai (81), Kowloon (76) and Kwai

Chung (47) Chest Clinics and Ruttonjee Hospital (10) (Fig. 2). The notes and radiographs of 183 of these 214 patients (86%) were obtained.

Details of the classification of patients is shown in Table 1. There was insufficient evidence to classify 15 of the 183 cases (group 4) due to insufficient culture or follow-up data. Of the remaining 168 cases, 28 (16.7%) had definite infection with NTM and evidence of progressive disease (group 1), 6 (3.6%) had persisting colonization without disease progression (group 2) and in 134 (79.8%) isolates were both transient and clinically insignificant (group 3). No patients were identified who were HIV positive.

PATIENTS WITH PROGRESSIVE DISEASE (GROUP 1)

The mean age of 28 patients with progressive disease was 59 years (range 29–84); 17 (61%) were men. Seventeen (61%) had suffered from pulmonary tuberculosis in the past with a variable degree of residual scarring or bronchiectasis. Fourteen of these had received anti-tuberculous therapy previously. Three further patients had underlying pulmonary disease (one silicosis, one emphysema, one non-tuberculous bronchiectasis). Only eight (29%) subjects had no pre-existing lung disease.

Table 1 Classification of disease (n=183)

Group	No.	Mean age	%male	Previous TB
Progressive	28	59 years	61%	61%
Colonization	6	57 years	83%	83%
Contaminant	134	55 years	66%	56%
(Not classified)	15	53 years	87%	66%
Total	183	56 years	66%	57%

The NTM organisms responsible are shown in Fig. 3. The commonest was *M. avium* complex which accounted for 15 (54%) of the cases of progressive disease. *M. chelonae* accounted for four cases, two of which were fatal. The outcome of patients with progressive disease is shown in Table 2.

Twenty-four of the 28 (86%) cases with progressive disease had at least one smear positive sputum sample in addition to repeated positive cultures.

PATIENTS WITH COLONIZATION (GROUP 2)

The mean age of patients with colonization was 57.5 years (range 16–78); five of the six were men. Only one had no pre-existing lung disease — the other five had been treated for previous infection with culture positive *M. tuberculosis*. Four had colonization with *M. avium* complex, one with an unclassified Runyon group 3 organism and one with *M. chelonae*. Five (83%) had at least one smear positive sputum sample.

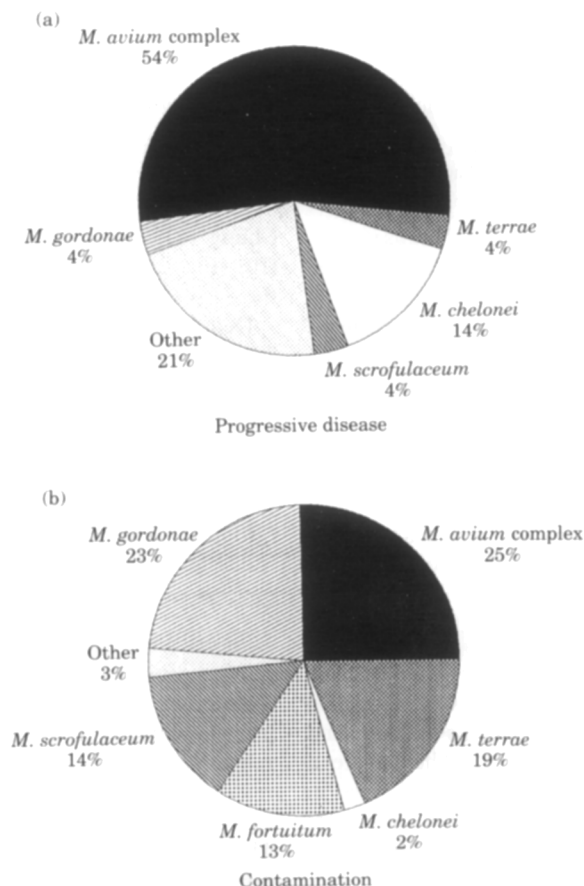


Fig. 3 (a) Non-tuberculosis mycobacteria causing progressive disease. (b) Non-tuberculous mycobacteria causing contamination.

Table 2 Non-tuberculous mycobacteria causing progressive pulmonary disease (group 1)

Organism	Number of cases	Outcome
<i>M. avium</i> complex	15 (52%)	1 progressive disease despite treatment 9 stable on treatment 5 stable after completing treatment
<i>M. chelonae</i>	4 (14%)	2 died 1 stable on treatment 1 stable after completing treatment
<i>M. gordonae</i>	1	Stable after completing treatment
<i>M. kansasii</i>	1	Stable on treatment
<i>M. terrae</i>	1	Progressive disease despite treatment
<i>M. scrofulaceum</i>	1	Stable after completing treatment
<i>M. szulgai</i>	1	Stable on treatment
Runyon group I	1	Died
Runyon group III	2	1 progressive disease despite treatment 1 stable on treatment
Runyon group IV	1	Progressive disease despite treatment

PATIENTS WITH CONTAMINATION (GROUP 3)

The commonest organisms responsible for contamination of sputum were *M. avium* complex (34 cases, 25%), *M. gordonae* (31 cases, 23%), *M. terrae* complex (25 cases, 19%), *M. scrofulaceum* (19 cases, 14%) and *M. fortuitum* (18 cases, 13%) (Fig. 3).

Of these, *M. gordonae*, *M. terrae* and *M. scrofulaceum* were rare causes of progressive disease, each causing one case in the study group. *M. fortuitum* caused no progressive disease in the study group. This suggests that the detection of these organisms on sputum culture is frequently non-significant.

In contrast to groups 1 and 2, only 3 of 133 (2.25%) patients with contamination (group 3) had organisms seen on direct smear.

Seven patients (5%) in group 3 had underlying malignancy involving the lung. In each case, NTM isolation was transient and there was no evidence of progressive pulmonary damage due to NTM.

Discussion

This study suggests that the majority of NTM isolates from sputum in Hong Kong are not clinically significant. The prevalence of progressive pulmonary disease associated with a positive sputum culture was found to be only 2.0 per 100 000. An estimate of 115 such cases would have been seen in the territory during 1990; these would represent nearly all patients with a positive sputum culture, since all such patients are under continuing follow-up and sputum samples are sent routinely for culture every 4–6 months in most cases.

This is the first study to document the prevalence and clinical significance of NTM isolation from sputum in an ethnic Chinese population. The fact that one laboratory processes all sputum specimens for the whole territory has allowed an accurate estimate of the overall prevalence of NTM isolation. The organization of the tuberculosis service in Hong Kong including storage of radiographs and the high standard of case-note documentation allowed accurate identification and categorization of nearly all patients.

The large number of apparently insignificant NTM cultures in 1990 may be due to a combination of factors. The prevalence of tuberculosis in Hong Kong dictates that a large number of sputum specimens are sent for mycobacterial culture each year, increasing the chance of isolating contaminating NTM organisms. Another factor might be the high prevalence of chronic cavitary lung disease caused by previous tuberculosis in the study population. These cavities might be intermittently colonized by NTM without deleterious effects in the majority of patients. However, it is possible that the transient sharp rise in the number of isolates of *M. terrae* and *M. gordonae* seen in 1990 was due to contamination of the sputum specimens in the laboratory. This is supported by the sudden rise in isolates of these organisms in 1990, and the persistence of high numbers of positive isolates of *M. gordonae* in 1991 (Fig. 1). In contrast, the rise in numbers of isolates of other NTM organisms was more modest. The low incidence of clinical disease due to *M. terrae* and *M. gordonae* would also support this hypothesis, there being only one case each of progressive disease in the study population.

The presence of acid-fast bacilli on direct smear appears to be the most useful indicator as to whether subsequent isolation of NTM represents true infection or contamination. Using χ^2 analysis, there is a significant difference in smear positivity rates between groups 1 and 2 (progressive disease/colonization) compared with group 3 (contamination) ($P < 0.0001$). However, there are no factors at presentation which distinguish between patients who have colonization and those with subsequent progressive disease.

It is possible that some of the cases classified as colonization were in fact very slowly progressive disease that was not detected during the follow-up period. However, many cases had been detected several years previously and followed for some years without evidence of disease progression.

M. chelonae has been considered a mainly contaminating organism when isolated in the sputum in other parts of the world (2,7). However, in this study four out of eight patients with this organism had progressive disease and two died. Isolation of *M. kansasii* appears to be uncommon in Hong Kong (Fig. 1), in contrast to some parts of Europe and the U.S.A. (2,3). Also, *M. malmoeense* and *M. xenopi*, although increasingly reported in these regions (3,8,9,10), were not found in this study.

It is more difficult to estimate the prevalence of extra-pulmonary disease due to NTM in Hong Kong partly because lymphadenitis is often treated surgically without microbiological confirmation and partly because laboratories not directly involved with the pulmonary service may not forward specimens of NTM to the reference laboratory.

This study highlights the frequency of NTM isolates from sputum that do not necessarily represent

clinical disease, and emphasizes the importance of examining trends in positive NTM cultures.

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